near the surface—never deep, as in the resistant type. The borders are generally narrow, slightly elevated, firm, grayish-white, and composed either of separate pearly nodules or of such nodules run together to form a ring or part of a ring. The base is sometimes fairly deeply excavated, as in Case V., but usually it is only a little below the level of the surrounding skin. It is sometimes bright red, and moist from exuded serum, but the exudation is never very great, and often dries to a scab, which falls from time to time, or which may be pulled off, leaving a moist, easily bleeding surface; or the base may be only delicate pink scar tissue. In the above series but one case of this type (Case VII.) recurred.

Before closing there is another class to be mentioned, for whom *x*-ray treatment is invaluable—a class dependent on the patient rather than on the type of disease. It includes that large group of cases in which any radical operation is impossible, is inadvisable, or is refused. Besides the frankly inoperable cases which every surgeon knows, and those whose horror of the knife is such that any cutting operation is out of the question, there are many patients who by reason of age or of bodily infirmity would be placed in much greater danger by an operation than they suffer from their disease. Case II. is a good example. He is a man of seventy-eight years, in good general health, but not strong enough to run the risk of a general anæsthetic. He is now, four months after his last treatment, absolutely free from all signs of recurrence. But even should the growth return there is every reason to believe, from his previous history, that it could at least be held in check, and long before he could suffer any inconvenience from it he will probably die from some intercurrent disease—as actually happened in Case XVIII. For such cases the safety, the convenience, and the painlessness of the method are its great advantages; and to these advantages we may add, if the lesions be superficial, a reasonable hope of permanent cure.

A STUDY OF ACUTE HEMORRHAGIC ENCEPHALITIS (STAPHYLOCOCCUS PYOGENES AUREUS).

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Following is a study of encephalitis in man, due to the staphylococcus pyogenes aureus. Parallel lesions have been studied in guinea-pigs, with a view to establishing the time limits and order of the acute inflammatory changes.

A text for the present work was afforded by some points of a case, previously reported at length,[1] of cortical hemorrhages ensuing upon subinfection with the staphylococcus pyogenes aureus during convalescence from scarlet fever in a boy aged five years. An abstract of this case follows:

CASE I.—*Abstract.* About five weeks after onset of scarlet fever, convalescence was interrupted by cerebral symptoms, and death occurred two weeks later (seven weeks after admission). The contractions and sensory symptoms began in the right leg and advanced during four days to affect the whole right side, including the face. The contractions were sharply defined (at one time alternating regularly with relaxations at intervals of about ten seconds) and limited in duration (a few minutes). Paralysis of the affected limbs ensued. During the last week the child was in the main unconscious (masking symptoms on left side).

At autopsy the organs and tissues showed little gross evidence of lesion, beyond desquamation of skin and fresh and pigmented hemorrhagic lesions in the cortex of both parietal lobes, with œdema of overlying pia mater.

Microscopic study showed an early bronchopneumonia and septicæmia (staphylococcus pyogenes aureus) and a purulent inflammation of foci in the parietal pia mater and overlying arachnoidal villi. Besides large areas of hemorrhage in the cortex, there was extensive development of cells phagocytic for polynuclear leukocytes, blood corpuscles, and fatty detritus. These phagocytes lay in meshes of the pia mater and in the adventitia of the short arteries of the cortical system. The phagocytosis was accompanied by solution and fatty changes of adjacent nerve tissues. Fatty changes in associated motor systems and early changes (axonal degeneration of anterior horn cells by Nissl method) in the lower motor systems.

The interpretation of Case I. is not wholly clear. Suspicion, however, attaches to the staphylococcus pyogenes aureus and its toxins for the production of some of the cerebral lesions. A study has therefore been made of further accessible cases of septicæmia and encephalitis associated with the staphylococcus aureus to find what aspects are held in common. Abstracts of these cases follow:

CASE II.—*Clinical History.* A. B., a girl aged twelve years, was admitted to Dr. G. C. Sears' service at the Boston City Hospital January 7, 1901. On entrance she was wildly delirious. Her head was retracted, and there was spasm of the posterior cervical muscles, with inability to flex the head. The pupils were widely dilated and failed to react to light. Both tonsils were enlarged, and the tongue bore a heavy white fur. There was a loud, rough, systolic murmur audible throughout the heart area, but at its maximum in the second left intercostal space and over the apex. The murmur was transmitted into the vessels of the neck, the axilla, and the back. There were a few moist rales at bases of lungs behind. The abdomen was everywhere tympanitic, and there was slight voluntary spasm of the walls. The reflexes were normal. Over outer aspect of right ankle, extending from a point 18 cm. above external malleolus to the heel, was an erythematous swelling, acutely tender and painful on passive motion. Below malleolus were three small pustules with incised (surgical) wound.

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[1] E. E. Southard and F. R. Sims. A Case of Cortical Hemorrhages following Scarlet Fever, Journal of the American Medical Association, September 17, 1904.

The origin of this condition is unknown. Four days before she had the first symptoms of her illness, chilly feelings and frontal headache. The next day small black spots were noted on the right foot, and an incision was made. The next day (third of the attack) she vomited after meals. Then gradually supervened the condition at entrance as above described.

The girl was fairly well developed, but poorly nourished. She is said to have had rheumatic fever at six years of age, scarlet fever at nine, measles at ten, and was just recovered (five weeks) from diphtheria. It is not possible to say what importance attaches to any of these events.

The day after entrance fresh inflammatory areas developed over the head of the fifth metatarsal bone of the left foot and the inner aspect of the left wrist. The leukocytes were but 10,000 per c.mm. The patient immediately vomited the food administered by nasal catheter.

The evening of the third day after entrance the patient died without notable change of condition.

Clinical Summary. Girl, aged twelve years, just recovered from diphtheria, with history of rheumatic fever, scarlet fever, and measles. Onset of attack, chilly feelings, and frontal headache, with development of purulent hemorrhagic areas on right foot, and vomiting two days later. Four days after onset, admitted in delirium, with suppurating wound of heel and heart murmur. Retraction of head. Dilatation of pupils, which failed to react to light. Development of fresh superficial inflammatory areas. Death eight days after onset of symptoms.

The autopsy was performed by one of us (E. E. S.) January 10, 1901. Following are the findings in the head:

Brain, weight 1200 gms. Dura tense, convolutions somewhat flattened. Density of brain about normal except right occipital lobe, which is semifluctuant. On section there is found near the apex of this lobe a rather firm, irregular mass of clotted blood, 3 cm. in greatest diameter. It reaches to within 1 cm. of surfaces of brain, but does not show externally. Around the clot is more or less fluid blood. The adjoining brain tissue for some distance is stained reddish-brown and is of soft consistence. The hemorrhage has extended into the right lateral ventricle, where fluid blood is present. A little is present also in the left ventricle.

Anatomical Summary. Wound of heel, with purulent infiltration of adjoining tissues; infective thrombus left ventricle wall; multiple abscesses of heart wall, kidney, adrenal, liver, spleen, intestines; diffuse small hemorrhages of lungs, kidney, epicardium; hemorrhages and softening of right occipital lobe; fatty degeneration of myocardium and skeletal muscles; chronic endocarditis (mitral); chronic adhesive pericarditis; chronic pleuritis of left lung and right apex.

Microscopic Findings. Cultures from the organs showed a septicæmia due to the staphylococcus pyogenes aureus. The growths were pure except from the kidney, which showed,besides the staphylococcus, an organism of the colon-typhoid group.

The histological examination of the various organs confirmed the diagnoses from gross findings. The lung shows small hemorrhages, chiefly without leukocyte reaction. The marrow of the femur is very cellular, containing numerous leukocytes of the mononuclear series, but very rare polynuclear leukocytes.

Special study of tissues from the brain was made by a variety of methods.

The subcortical lesion in the occipital lobe shows wide sheets of clear, well-preserved blood, with occasional polynuclear leukocytes and several foci of staphylococci, both free and within cells. The hemorrhage penetrates the cortical tissue along lines of least resistance between the radiating bundles of nerve fibres. Occasionally large vessels from the cortical system run free through the blood, with the adventitial meshes dilated with polynuclear leukocytes and occasionally embraced by areas of coarse fibrin. Near the vessels there occur purulent areas, with fatty changes, pigment, fat-containing and pigment-containing phagocytes, and without notable evidence of repair. Adjacent to the hemorrhagic areas the myelin, as a rule, stains perfectly; but a few fibres are represented in Marchi sections by linear collections of black dots. The nerve cells occasionally show changes, as a rule attributable to swelling or shrinkage due to œdema. These changes are scarcely more marked near the hemorrhage than remote from it.

CASE III.—*Clinical History.* H. H., a man, aged twenty-two years, was admitted to Dr. G. B. Shattuck's service at the Boston City Hospital, December 5, 1903. On entrance he was unconscious and restless, with flushed cheeks and equal, contracted pupils, reacting sluggishly to light. There was slight rigidity and retraction of neck. The abdomen was slightly retracted and rigid, with tenderness over pubes. The legs were flexed and rigid. The hands and feet were blue, and there were irregular hemorrhagic areas about thumbs and over outer surfaces of both feet and the toes.

The knee-jerks were normal. Kernig's sign and Babinski's sign were absent.

The attack had begun the day before, with increase in frequency of micturition and general discomfort. The physician, Dr. C. L. Knight, had forthwith suspected cystitis, as he had had the patient under treatment for some time for urethritis. In the afternoon of the day before admission the patient complained of severe pains in various parts of the body, especially the thumb and ankle. Nausea, vomiting, and delirium followed.

The day after admission (the third day of the symptoms) the patient died, without marked change of condition. The pulse, at first of moderate rate, later became rapid, small, and easily compressible. Cyanosis increased. The chest became filled with moist rales. The ecchymoses of the extremities slowly increased in extent. The pupils became widely dilated and still reacted sluggishly to light. The reflexes remained as before; there was some question whether Babinski's sign was present.

Clinical Summary. Man, aged twenty-two years, with history of treatment for urethritis. Onset of attack with increased frequency in micturition and malaise. Later in the day various focal pains, nausea, vomiting, delirium; cyanosis; ecchymoses on thumb, ankles, and toes. Pupils at first contracted, before death dilated. Death on the third day.

Autopsy Findings. The autopsy was performed by Dr. R. L. Thompson and one of us (E. E. S.) December 7, 1903. The findings in the head were:

Head. Hair dark and fairly thick. Scalp normal. Cranium of the usual thickness. Dura externally smooth and tense. Sinuses contain fluid blood with cruor clot. Pia over left hemisphere almost dry, and tightly stretched over flattened convolutions and effaced sulci. There are a number of irregularly distributed ecchymoses, varying in diameter from a pin's head to 0.5 cm. or more, rarely 0.75 cm., either within meshes of pia at lips of sulci or shining through from cortical substance. In the region of the left supra-angular gyrus are two well-defined ecchymoses, with irregular and re-entrant borders (0.5 cm. and 0.75 cm. in diameter, respectively), containing in the middle pinhead foci of frank, yellowish-green pus. The pus has not broken through the pia. Pia over right hemisphere contains a slight amount of clear fluid, but is externally almost dry. Effacement of sulci by pressure has just begun. Pia on both sides shows a well-marked injection, with minute, tree-like tracery in the superficial cerebral venules. About some ecchymoses are delicate pink areas of diffused blood pigment (some of which may be of post-mortem origin). Vessels at base normal.

Cerebrum. The core of the left occipital lobe is replaced with a walnut-sized mass of loosely clotted blood, resting in a bed of moist, grumous, pinkish-gray detritus. Beyond the zone of disintegration is œdematous white matter, with distinct puncta cruenta and minute hemorrhages. The cortex of the occipital pole is destroyed, and the hemorrhage points also upon the posterior horn of the left lateral ventricle, into which has oozed several cubic centimetres of blood, now clotted *in situ*, with a little staining of posterior portion of choroid plexus. There is no gross evidence of old abscess or other lesion than hemorrhage in this area. It is probable that the hemorrhage is from a medullary branch or branches of the cortical arterial system.

The core of the right occipital pole shows a similar area of hemorrhage (from the medullary branch of the cortical arterial system), thimble-shaped, giving destruction chiefly of white substance with a small portion of cortex. The pia is just tangent to the lesion, which is, therefore, scarcely evident from without.

The substance elsewhere is slightly moister than usual, and both cortex and white matter contain fairly numerous, pinhead, purplish areas of hemorrhage, without evidence of pus. These areas are somewhat more frequent on left side. The substance on section shows a slight retraction of white matter (or release of tension in gray?) and a diffuse appearance somewhat suggestive of encephalitis, but there is no relatively normal white substance with which to compare.

The basal ganglia and lower system are spared from lesion. There are a few ecchymoses in the cerebellum.

Brain. Weight 1265 gms.

Anatomical Summary. Acute endocarditis; acute pericarditis; multiple abscesses of liver, kidney, and thyroid; infarcts of small intestine; acute splenitis; hyperplasia of mesenteric lymph nodes; acute fibrinous pleuritis (left); œdema and congestion of lungs; acute purulent bronchitis; interstitial orchitis; œdema and congestion of brain; multiple ecchymoses of white and gray matter; abscesses of cortex; hemorrhages into occipital poles (probably from medullary branches of cortical arterial system).

Microscopic Findings. Cultures from heart's blood, pericardium, mitral valve, liver, spleen, kidney, right centrum semiovale, left occipital lobe, and abscess on heel showed staphylococcus pyogenes aureus.

Histological examination of the organs of the trunk showed in the main the lesions diagnosed from gross appearances. The kidney shows a focal chronic interstitial process.

In the subcortical regions of certain foci in the cerebrum and the cerebellum are well-defined abscesses of a characteristic type. A central colony of staphylococci is surrounded by polynuclear leukocytes in a zone, which is in turn surrounded by a zone of fresh hemorrhage. These areas are sometimes a millimetre in diameter, but are, as a rule, merely punctiform. Beyond the lesions there is usually no sign of tissue reaction.

CASE IV.—*Clinical History.* M. M., a woman aged forty-two years, was admitted to Dr. G. C. Sears' service at the Boston City Hospital March 14, 1902. On entrance she was mildly delirious. There was well-marked sclerosis of all palpable arteries, and the heart showed at the apex short systolic and presystolic murmurs, heard also in axilla and back; a systolic murmur was audible at base and in aortic and pulmonary areas. The right lung was dull below the fifth rib in the axillary line (respiration and vocal resonance distant, tactile fremitus diminished). There were friction sounds opposite the right fifth rib. The left base showed many moist rales. Abdomen, dull in flanks, showed fluid wave. There was considerable œdema of ankles and legs. The pupils were equal and reacted normally.

The woman is said to have had influenza three years before, after which she had suffered from dyspnœa, palpitation, and frequent micturition. The menopause had occurred three months before onset of present illness. For four months she had had a slight cough. A week before entrance she had taken to bed with a sharp attack of pain in the right chest, followed by rapid and progressive increase in dyspnœa and increase of cough, with frothy expectoration.

After admission her condition grew worse; she became noisy and garrulous and required restraint. A week after admission she got out of bed during the night and injured her right eye. The upper lid had to be incised some days later, and two drachms of pus were evacuated. Constipation set in, with palpable fecal masses over abdomen. The orbital suppuration grew gradually better, but on the twenty-third day after admission (two weeks after injury to eye) an erysipelas-like condition developed about the eye. Thenceforward the patient gradually failed, and a week later died.

Clinical Summary. Woman, aged forty-two years, just after menopause, with arterial and cardiac sclerosis. Pleurisy with effusion, gradually deepening delirium, injury to eye with suppuration (a week after admission, two weeks after onset of pleurisy), and constipation. Death three weeks after injury to eye, a week after development of erysipelas-like condition about eye, two days less than a month after admission.

Autopsy Findings. The autopsy was performed by Dr. W. R. Brinckerhoff April 14, 1902. The findings in the head were:

Brain. Weight, 1270 gms. Dura and sinuses normal.

Middle Ears. Normal.

On the external aspect of the right temporal lobe is a small abscess (3 mm.) surrounded by a zone of injection. Similar smaller abscesses are present over the vertex. On section, ventricles contain considerable amount of clear, straw-colored fluid. The substance of the cerebrum appears normal. Cerebellum normal. In the middle of pons is a circular area 6 mm. in diameter, which is somewhat soft and of a black color. This area is sharply circumscribed. Its greatest diameter is lateral, not appearing in the adjacent sections 5 mm. apart. The surrounding brain substance appears normal.

Anatomical Summary. Pleurisy with effusion (right side); hydropericardium; multiple abscesses of heart, kidneys, spleen, lung, and brain; ulcerative colitis and proctitis; chronic diffuse nephritis; acute cystitis; uterine fibromyoma; general arteriosclerosis; chronic splenitis; small hemorrhage in pons.

Microscopic Findings. Cultures from liver, spleen, and kidney showed pure growths of staphylococcus pyogenes aureus. Histological examination of the various organs confirmed the diagnosis of septicæmia. No cultures were taken from the brain abscesses, which were saved entire for histological purposes; but there can be no doubt of the relation of the staphylococcus to the abscesses. The special points in the histology of this case are brought out in the following:

The lesions beneath the pia mater of the temporal lobe, for example, consist of a central colony of staphylococci in and about a vessel which is surrounded by a zone of polynuclear leukocytes, often phagocytic for the bacteria. Among the polynuclear leukocytes are numerous larger phagocytes, now of the compound granule type, elsewhere containing chromatic material derived, as a rule, from polynuclear leukocytes. The large phagocytes sometimes contain bacteria as well as remains of tissue cells. Outside the zone of polynuclear leukocytes is a broader zone, consisting almost purely of cells of the phagocyte group, here in most instances of the compound granule type. Beyond these zones of nucleated cells is a zone of pure and well-preserved blood. There is nowhere any notable amount of fibrin. There are in many places small vessels plugged with staphylococci, some of which have grown post-mortem.

The sections from the pontine lesion are of note by reason of the juxtaposition of the fresh hemorrhagic lesions with an older cystic lesion. The older lesion consists of a small cavity, about 2 mm. in diameter, lined by a condensed layer of neuroglia and filled with large, vacuolated phagocytes and granular material. The neuroglia lining is interrupted in places by slender projections due to vessels invested by a thin layer of oval, fibrillated glia cells. The fresh lesions show blood free in the meshes of the tissue, with here and there a large phagocyte and polynuclear leukocyte and without notable amounts of fibrin. The surrounding tissue shows no reaction beyond an increase in the volume of the cell bodies in some neuroglia cells.

CASE V.—*Clinical History.* J. C., blacksmith, of middle age, was admitted to Dr. A. L. Mason's service at the Boston City Hospital December 3, 1897. He was brought to the hospital delirious and unconscious in an ambulance, having fallen in the street.

Physical examination showed the left pupil slightly larger than the right, knee-jerks absent, pulse feeble but regular, chest slightly hyperresonant, pleural rubs in left axilla and lower back, and a temperature of 104°. The urine showed 0.5 per cent. albumin. The patient died the day after admission without change of condition.

Autopsy Findings. The autopsy was performed by Dr. F. B. Mallory December 4, 1897. The findings in the head were:

Brain. On the right side of the pia 3 cm. from the median fissure, and in the sulcus just back of the fissure of Rolando, were three, minute, yellowish specks, apparently miliary abscesses. The surrounding brain tissue was œdematous and swollen and the pia contained minute hemorrhages. In the substance of the brain no lesions could be found anywhere.

Middle ears normal.

Sinuses of nose and the antrum of Highmore on each side were all normal.

Anatomical Summary. Septic infarctions of lungs; metastatic abscesses of kidneys and meninges; acute fibrinous pleurisy; chronic adhesive pleurisy; congestion of lungs.

Microscopic Findings. Cultures from organs of the trunk showed pure growths of the staphylococcus pyogenes aureus, except that from the kidney, which showed also an organism of the colon-typhoid group.

Histological examination confirmed the diagnosis made from gross appearances. The liver shows some cellular infiltration of the portal spaces and central congestion.

The histological picture presented by the brain varies from a simple meningitis to a diffuse meningoencephalitis. The simple meningeal inflammation consists of an exudate of polynuclear leukocytes, more thickly into the proximal meshes of the pia mater. There is strikingly little blood and a small amount of fibrin in this lesion. There are fewer meningeal phagocytes than usual; but a few lymphatic clefts are filled with such cells containing fragmented polynuclear leukocytes. The exudate follows the cortical arteries into the brain substance in some cases as far as the white matter. The subpial neuroglia and the pyramidal cell layers are for long distances dotted with polynuclear leukocytes of fairly even distribution. It is unusual to find polynuclear leukocytes in apposition with nerve cells. The nerve cells are slightly swollen. The bodies of the neuroglia cells are, as a rule, invisible; but some of the cells of the subpial layer approach the astrocyte in type.

CASE VI.—*Clinical History.* A. M., an Irish woman aged thirty-three years, was admitted to Dr. J. N. Coolidge's service at the Boston City Hospital June 15, 1904. On entrance she was delirious, half-conscious, and unable to answer questions. There was convergent strabismus and a choreiform or athetoid tendency to co-ordinate movements of both arms. Nothing further was discovered in the physical examination to throw light on the condition. The present illness was said to have lasted ten days, setting in with vomiting, which continued for five days. The strabismus was developing meanwhile, and the twitchings became well marked. She was sleepless and complained of soreness in the abdomen. For years she had been addicted to the use of alcohol, often to excess. The patient died five days after entrance. The choreiform movements persisted until death. The convergent strabismus became more marked. Stiffness of neck developed. The reflexes remained normal.

Clinical Summary. Woman, aged thirty-three years, with history of abuse of alcohol, died in delirium fifteen days after onset of an attack of choreiform character, with convergent strabismus, insomnia, and normal reflexes. Onset with vomiting, lasting five days.

Autopsy Findings. The autopsy was performed by Dr. S. B. Wolbach June 21, 1904. The description of the head by one of us (E. E. S.) follows:

Head. Scalp normal; skull symmetrical; frontal suture effaced. Superciliary ridges and frontal eminences ill-defined. Calvarium opaque by transmitted light and everywhere moderately thickened. The thickening affects chiefly the inner table, and is least marked at the bregma, where the internal surface presents a shallow, diamond-shaped depression corresponding to the anterior fontanelle. The frontal bone shows marked symmetrical thickening, which transforms inner arc to an oblique flat surface, on which there is a slight groove for the superior longitudinal sinus and a few narrow depressions for the meningeal vessels. At a point 4 cm. from the orbit the bone is 1.5 to 2 cm. thick. The diploë is nowhere well marked. The frontal bone is ivory-like on section and of the consistence of the petrous bone. Dura normal. The dura beneath frontal bone is readily separable from the inner table. Sinuses and meningeal veins contain fluid blood. Pial vessels everywhere injected. Arachnoidal villi well developed. Pia of vertex œdematous. Substance moist. Everywhere elastic except in an ill-defined area, including second right temporal convolution. The cortex and underlying white of this region are plastic and readily crushed; the puncta cruenta of the white matter are distinct, and there are a few minute, perivascular hemorrhages. Co-ordinate areas in the left hemisphere are equally moist; but the gray matter does not bulge from the plane of section. The rest of the centrum semiovale shows no more than œdema.

The frontal convolutions are fairly symmetrical. There is no microgyria and no narrowing of gray matter, but there is a slight *increase of consistence in the frontal gyri on comparison with, for* instance, the occipital gyri. The frontal and especially the prefrontal region as a whole may be looked on as undersized. Rest of encephalon and spinal cord show less œdema than the hemisphere and no further gross lesion.

Middle ears normal.

Anatomical Summary. Œdema and congestion of lungs; chronic fibrous pleuritis (left); œdema of pia; cerebral œdema; focal softening of right second temporal convolution (encephalitis); frontal lobes undeveloped; thickening of cranium (most marked in frontal bone).

Microscopic Findings. Cultures from organs of the trunk remained sterile. Culture from the white matter beneath the second right temporal convolution showed staphylococcus pyogenes aureus, together with a few colonies of similar appearance which never assumed a golden-yellow color (staphylococcus pyogenes albus?). A culture of the staphylococcus pyogenes aureus derived from this case was used in a portion of the inoculations described below.

Examination of the organs of the trunk showed nothing adequate to account for the history of the case. The lung shows a few *Herzfehlerzellen* in some alveoli and a few bronchi plugged with polynuclear leukocytes in good preservation and without bacterial inclusions. The spleen shows an unusually high percentage of polynuclear leukocytes and fairly numerous eosinophilic leukocytes in the pulp, but is otherwise not remarkable. The liver is slightly fatty; some of the cells central in the lobules are lace-like. The kidney shows a few slender casts in the tubules of the pyramids. Otherwise both the organs mentioned and the others examined show little that is noteworthy.

Co-ordinate places in the hemispheres were examined to detect the extent and nature of the inflammatory process suggested by the gross appearances and the bacterial findings. The two sides are distinguished by the fact that, in the section taken from the cortex and white matter of the right temporal lobe, there are numerous small collections of blood globules, with a few polynuclear leukocytes lying in the meshes of the arterial adventitia. There seldom occur, however, hemorrhages of any great volume. Blood rarely occurs free in the tissue. On comparison with tissue from the opposite hemisphere it is found that very many more distended capillaries have become visible in the cortex and notably in the subcortical region of the right temporal lobe. Several of these capillaries are found packed with polynuclear leukocytes. The neuroglia shows no pertinent differences on the two sides; the subpial glia of the left hemisphere appears denser in structure than in the right in the places examined. Numerous nerve cells are contracted and somewhat densely staining by several of the technical methods employed (eosin and methylene blue, aniline blue connective tissue, and phosphotungstic-hæmatein methods, for example). These cells are possibly more numerous in the left hemisphere than in the right in the places examined. These latter changes are certainly not beyond the range of artefact and are scarcely entitled to specific importance on account of the omnipresent œdema. Yet these cells recall the cells found in certain foci of our experimental material. The cerebellum and the rest of the nervous system as far as examined showed no noteworthy lesion. A few capillaries in the choroid plexus contain numerous polynuclear leukocytes; there is a much smaller number outside the capillaries and none beyond the ependyma.

GENERAL CLINICAL SUMMARY. From the histories detailed above the following *rêsumê* has been drawn:

Three of the patients were male, three female. Their ages varied from five to fifty-five years.

In every case, excepting Case V., whose past is unknown, there is a history of antecedent disease; thus Case I. was convalescing from scarlet fever; Case II. was five weeks recovered from diphtheria and had a chronic endocarditis of long standing; Case III. was under treatment for chronic urethritis; Case IV. had pleurisy with effusion and was but three months beyond the menopause, and Case VI. had a history of excess in alcohol of many years' duration.

The onset was in three cases sudden (hemiparesis and unilateral convulsions in Case I.; chilly feelings and frontal headache followed by ecchymoses in Case II.; malaise, manifold pains, ecchymoses, and cerebral symptoms in Case III.). Case V., in which the onset is unknown, was in all ways fulminant. In Case IV. the symptoms gradually supervened upon the pleurisy and the orbital suppuration. Case VI. showed a gradual onset.

The syndromes as a whole were of pronouncedly cerebral type in Cases I. and VI., of meningitic trend in Cases II. and III., of septicæmic character in Case IV. Septicæmia could be suspected in all three cases (II., III., IV.) in which superficial ecchymoses or suppuration became prominent.

The temperature varied for the various cases: at times 103° and 104° for cases III. and V.; the temperature in cases II., IV., and VI. was never high and frequently subnormal.

The pulse was in no case subnormal, and, as a rule, ranged above 100. The respirations were, as a rule, increased.

The duration of the encephalitic symptoms cannot in all cases be closely reckoned: Case III., three days; Case IV., one week (after development of erysipelatoid condition) or three weeks (after injury to eye); Case II., eight days; Case I., two weeks; Case VI., fifteen days; Case V., unknown. Thus those cases were of longer duration in which the cerebral syndromes were most clearly marked.

GENERAL ANATOMICAL SUMMARY. Of the gross findings at autopsy the following are to our present purpose: chronic lesions which might correspond with greater likelihood of bacterial infection were found in several cases; thus, the remains of scarlet fever in Case I., chronic endocarditis in Case II., arteriosclerosis in Case IV.

The phenomena of general infection were found in Cases II., III., IV., and V. Comment is made below upon the correlation of pulmonary lesions with our cases.

The distribution of the brain lesions is as follows:

Four cases (I., II., III., IV.) showed areas of frank and somewhat voluminous hemorrhage, as a rule involving primarily the subcortical region (of the vertex in Case I., of the occipital lobes in Cases II. and III.), and in Case IV. affecting the pons.

Three cases (III., IV., V.) showed multiple ecchymoses and small abscesses of the cortex or subcortical region, with or without gross evidence of surrounding œdema.

In three cases (I., V., VI.) œdema of pia mater was remarked.

In two cases (II. and III.) there was noted an effusion of blood into the lateral ventricles; and in these cases the convolutions were flattened.

In two cases (IV. and VI.) in which the temporal lobe was involved the middle ears showed no lesion. The mucosæ of the head play no such role in this kind of encephalitis as in the massive brain abscesses made familiar by Macewen.

General Summary of Microscopic Findings. The staphylococcus pyogenes aureus was found in all cases in culture postmortem, generally distributed in five cases, in the brain alone in Case VI. The diagnosis of general infection, at least at the time of death, seems warranted in the first five cases. Case VI., in all ways unusual, may possibly be interpreted as showing the first stage of a massive brain abscess; but the middle ear showed no lesion at autopsy. The atria of infection remain obscure in Cases V. and VI. In Cases II., III., and IV. acute endocarditis was found; and, although in none of these cases is the chain of evidence entire, there were present in all three adequate primary lesions (suppurating surgical wound in Case II., chronic urethritis in Case III., colitis in Case IV.).

The microscopic findings in the organs at large call for little comment. Focal pulmonary lesions were either grossly prominent or made out microscopically in all six cases. There was pus in the bronchi of Cases III. and VI., bronchopneumonia in Case I., and there were septic areas of hemorrhage in the lungs of Case II., septic infarction in Case V., and multiple abscesses in Case IV. This coincidence of pulmonary and brain lesions is certainly of clinical importance. A similar coincidence was noted at least as early as the sixties of the last century.[1] Compare also the production described below of meningitis and meningoencephalitis in the guinea-pig by intrapulmonary inoculations. We are not prepared at present to regard this coincidence as a matter of cause and effect.

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[1] Biermer, Zur Theorie und Anatomie der Bronchienerweiterung, Virchow's Archiv, 1860, xix. S. 244.

The microscopic findings in the brains of this series of cases present more features in common than the gross findings. Thus, whereas miliary abscess, punctiform or massive hemorrhage, and ill-defined red softening form quite diverse gross pictures, the microscopic pictures form unitary series or are well-nigh interchangeable.

It is, moreover, by no means scholastic to insist that too close lines cannot be profitably drawn between meningitis and encephalitis. The word "extension" has gained so wide a vogue that one forms the idea that, although a process may extend, the diagnosis somehow should not extend *pari passu.* Meningitis by extension from abscess and encephalitis by extension of pial inflammation are processes of importance, though charged with being merely secondary. It is these secondary phenomena, in especial the encephalitic ones, which, in the cured cases, may afford a basis for our so mysterious scleroses.

The inflammation of meninges and cortical and subcortical substance in man produced by the staphylococcus pyogenes aureus is distinctively hemorrhagic. Very little fibrin is formed in these lesions. The bleeding continues in some cases until stopped by intracranial pressure. Small vessels are, as a rule, affected.

The typical picture is of a central colony of staphylococci in and near a vessel surrounded by zones of polynuclear leukocytes, large phagocytic cells, and blood. Dying nerve cells are sometimes included in the lesion. The neuroglia cells are slightly active about some of the lesions. Fibril production is absent. The myelin sheaths stain well by Weigert to the edge of the lesions, but show fatty changes in Marchi preparations, for a short radius round about. Prominent in these lesions are the fat-containing and leukocyte-containing phagocytes of the type so often found in all kinds of cerebral lesions. The accumulation of these was in no other case so massive as in Case I.; but they are omnipresent. Their frequency and distribution are such that many foci of these lesions look, in accordance with our usual ideas, to be of long standing.

EXPERIMENTAL MATERIAL. As supplement to the histological work on the lesions in man, a series of inoculations of the staphylococcus aureus was made in guinea-pigs and rabbits. Several strains of staphylococci were used, derived from various lesions, including the focus in Case VI. It was found best to employ one species of animal for serial work; and the guinea-pig was chosen. It is easy to include in single sections meninges, substance, and ventricle of the guinea-pig brain. Several methods of inoculation were employed, as beneath the skin, into the lung, through the ear-plate, and beneath the dura. The guinea-pigs stood the inoculations well and, after recovery from chloroform anæsthesia, as a rule showed no sign of disease up to the time of examination. In some cases they were overwhelmed by the septicæmia. The fatal results are apparently more a matter of individual pig than of culture. The most convenient method was found to be the method by intrapulmonary injection.

By intrapulmonary injection of 0.5+ c.c. of a twenty-four-hour bouillon culture of the staphylococcus of the strains used one is almost certain to produce exudation into the meninges of the guinea-pig. Of this there will probably be no clinical evidence. But examination of the brains of the pigs at suitable intervals will show lesions of fairly rapid evolution. These inoculations have been controlled by subdural inoculations, with examination at similar intervals.

As early as six hours *after intrapulmonary inoculation* the meninges may show evidence of diapedesis of blood and exudation of polynuclear leukocytes of quite focal character. The ependyma remains clear, and no changes can be detected in the brain substance.

By twelve to fourteen hours after inoculation exudation through the ependyma is likely to be well under way.

Twenty-four hours after inoculation the vessels are injected, and blood and occasional polynuclear leukocytes are likely to be found in the pial meshes. The chief sign of inflammation, however, is the frequent demonstration in the vessels of a row or thin lining of leukocytes in the inert layer.

In one instance after intrapulmonary injection the guinea-pig immediately became paraplegic and was killed after twenty-four hours. The brain showed ependymitis, very marked meningitis, and the most extensive exudation of leukocytes into the brain substance which we were able to procure in the intrapulmonary inoculations. In this case leukocytes were very frequently seen in juxtaposition with the small pyramidal nerve cells. The same phenomenon was found later in the intrapulmonary series (although never so markedly as in this case) and is focally present in several instances in cases of subdural inoculations examined after two or three days. It is perhaps not necessary, in accounting for this occurrence of leukocytes near nerve cells, to invoke a richer lymph system for the guinea-pig brain than for the human brain. Possibly the leukocyte can more easily wander through the substance of the guinea-pig brain because it is less densely fibrillar than that of man.

Forty-eight hours after inoculation, the emigration of leukocytes into the tissue beneath the ependyma is already marked, and numerous examples can be found of leukocytes in apposition with nerve cells.

The cases examined three days after inoculation show meningitis, encephalitis, and ependymitis at their height. The controls by subdural inoculation show far more intense diffuse processes. The three-day subdural material can be recommended for study of the cells in the lesions produced by this organism.

In material examined four and five days after inoculation the exudate is already altered by the appearance of fairly numerous cells of the lymphocyte series and a number of cells phagocytic for cell detritus.

Six days after inoculation the lesions found are meningitis and pyocephalus, due largely to exudation from the choroid plexuses. The cells found are chiefly of the polynuclear amphophile type. Mononuclear cells phagocytic for leukocytes occur. The meningitis is rarely so voluminous as the ependymitis. Numerous polynuclear leukocytes follow the cortical vessels; and it is not unusual to find leukocytes of the amphophile type in close apposition to nerve cells, as well as free in the tissue of the upper cortical layers.

The brain of the guinea-pig nine days after inoculation shows little exudative process except about certain vessels, where rare polynuclear leukocytes occur with fairly numerous cells of the mononuclear series. Occasional cells phagocytic for chromatic material occur, besides a few pigment-bearing cells. The exudate is, as a whole, slight.

Few traces of inflammation are demonstrable in the brain of a guinea-pig one month after inoculation. The brain substance shows no alteration beyond a few areas of chromophilic nerve cells mentioned below. Neuroglia fibrillæ are demonstrable beneath the pia, but in quantity which is within the normal limits for the guinea-pig by the methods used. The ependyma shows no change. The pia mater contains a few pigment-bearing phagocytes, a few lymphoid and plasma cells, and relatively many eosinophilic polynuclear leukocytes.

The examinations were throughout controlled by cultures from various organs, the brain, and the site of operation in the subdural inoculations. A surprising proportion of negative cultures was obtained from the brain even where lesions of the appropriate age could be determined. The tenuity of the lesion makes searing risky. Perhaps cultures from the ventricle are preferable in cases where the process has reached the ventricle. The above descriptions have been founded on cases in which the bacterial diagnosis was secure. The organs of the trunk were examined in many cases to make sure of the pyæmia.

Mention may be made of a frequent lesion in the guinea-pig brain which remains obscure. To be distinguished sharply from the focal occurrence of condensed, deeply staining nerve cells, and from the occurrence in compressed material and at the edges of some sections of groups of similar cells which are more or less clearly a product of technical error, are certain foci of contracted, angular or subangular, deeply staining nerve cells of the cortex. In one case there were deposited in the cell bodies of one of these chromophilic foci dots staining by the phosphotungstic-hæmatein method. These foci of chromophilic cells occur, as far as we have yet found, without definite relation to the bacterial inoculations, but are not characteristic of the brain of normal pigs. The process is a little more frequent in groups of Purkinje cells.

RESUME. 1. The staphylococcus pyogenes aureus produces in the meninges and brain substance of man a type of inflammation in which hemorrhage is prominent.

The picture post-mortem in man varies from red softening or multiple ecchymosis and small abscess to frank and sometimes voluminous hemorrhage. The site of election for the hemorrhagic lesions is the subcortical region, supplied by the long or medullary branches of the cortical vascular system.

The histological picture varies from diapedesis and slight leukocyte emigration to abscess and acutely destructive hemorrhage with phagocytosis. Collections of mononuclear cells phagocytic for cells and cell detritus often quite obscure the acute inflammatory appearance of the lesion.

Six fatal cases in man were examined, all but one cases of general infection with the staphylococcus aureus.

A history of antecedent disease was the rule. The syndromes, which were chiefly of sudden onset and rapid course (three to fifteen days), were pyæmic, meningitic, or cerebral in type. The cases of slower course were the most plainly cerebral.

2. The staphylococcus pyogenes aureus produces in the brains of guinea-pigs an inflammatory process which tends to subside within a limited period (two weeks), and, as a rule, remains without clinical signs throughout.

No hemorrhages other than miliary perivascular ones were observed in the guinea-pig. The lesions are seldom grossly evident.

The cell pictures are of meningitis (discernible in six hours), ependymitis (twelve to fourteen hours), and exudation into the brain substance (twenty-four to forty-eight hours).

The four and five day cases show numerous cells of the lymphocyte series as well as mononuclear cells phagocytic for exudative cells. Examples of such phagocytic cells have been found as early as twenty-four hours after inoculation.

The exudation into the meninges is discernible earlier, and its traces are demonstrable later, than are the processes in the ependyma and the encephalon; but the meningitis is never so extensive or striking a process as the encephalitis or the choroiditis.

In two weeks to a month there is little sign of the previous infection.

3. The staphylococcus pyogenes aureus, of the strains and in the doses experimentally used, produces in the guinea-pig a curable encephalitis, that is a process which in logic is termed reversible. The same organism produced in our human cases extensive

brain lesions which surely look as a group irreparable. Perhaps, however, there are in man also certain cases of encephalitis which reverse themselves, and which in their course are taxed with being "functional" diseases and furnish "functional" symptoms during and after tissue repair.

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PRIMARY SPLENOMEGALY—GAUCHER TYPE.*

REPORT ON ONE OF FOUR CASES OCCURRING IN A SINGLE GENERATION OF ONE FAMILY.

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Clinical (Dr. N. E. Brill). Under the caption of primary splenomegaly have been heaped together indiscriminately a large variety of non-leukæmic enlargements of the spleen developing with or without anæmia. Osler, in an attempt to establish order out of chaos, suggested calling the cases of enlarged spleen associated with an anæmia of the chlorotic type and with hemorrhages, but unaccompanied by a leukocytosis, splenic anæmia, adopting as the cognomen the term first used by Griesinger for the splenic variety of Hodgkin's disease. He insists that these cases in their evolution present a terminal stage characterized by secondary cirrhosis of the liver associated with jaundice and ascites, which Banti described as constituting a disease *sui generis*, and which cases have been known as those of Banti's disease. But even with Osler's limitation, under the term of splenic anæmia, there have been associated diverse splenic enlargements, differing both in their clinical and pathological conditions, such as the cases described by Sippy,[1] Osler,[2] Rol-

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